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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,059	10/25/2001	Craig Basson	955-12	9868

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/027,059	Applicant(s) Basson
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 22, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above, claim(s) *9-69* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed April 22, 2003 (Paper No. 10) in response to the Office Action of March 25, 2003 (Paper No. 9) is acknowledged and has been entered. Claims 1-69 are pending in the application and Claims 9-69 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-8 are currently under prosecution.

2. The response (Paper No. 10) to the restriction requirement of March 25, 2003 has been received. Applicant has elected Group I, claims 1-8 for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Specification

3. The specification on page 1 should be amended to reflect the status of the parent provisional application. Appropriate correction is required.

4. Spelling error informalities have been identified in the specification. For example, "DESCRIPTIION" on page 4, para 0019. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where these errors may be found. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall

set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 1, 2, 4, 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated TBX5 protein fragment isolated from SEQ ID NO:1, a TBX5 protein fragment comprising amino acids 56-100 of SEQ ID NO:1, does not reasonably provide enablement for a TBX5 protein fragment comprising a translated 5' T-box sequence capable of binding to the major groove of target DNA and lacking a translated 3' T-box sequence capable of binding to the minor groove of target DNA, said fragment derived from a human, wherein the fragment lacks the sequence comprising amino acid 198 to the C-terminus of SEQ ID NO:1, a TBX5 fragment which comprises an amino acid sequence at least 60%, 80%, 90% - 98% identical to amino acids 56 to 100 of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 6-8 are drawn to a TBX5 protein fragment which comprises an amino acid sequence at least 60%, 80%, 90% - 98% identical to amino acids 56 to 100 of SEQ ID NO:1. The specification teaches that human wild-type TBX5 protein includes a T-box sequence that begins with amino acid 56 and ends with amino acid 238 of SEQ ID NO;1. A useful 5' T-box sequence capable of binding to the major groove of target DNA begins at approximately amino acid 56 of the human protein of SEQ ID NO:1 and contains a sufficient number of residues to inhibit cellular proliferation (p. 5, 0024). The invention includes functional homologs of the protein

fragments described wherein homologs of a protein fragment are considered to be functional homologs if the homolog maintains at least some activity of the protein fragment (p. 6, 0028). The homolog can be a substitution, addition or deletion variant (p. 6, 0030). An example of the instant fragment results from a naturally occurring mutation in the TBX5.2 clone described in Basson et al, Nature Genetics, 1997, 15:30-35) which causes a deletion at position 593 of the complete wild-type coding sequence for human TBX5 (p. 7, 0033). The invention provides a method of inhibiting the proliferation of a cell comprising administering the fragment described (p. 11, 0048). The method is especially effective for inhibiting proliferation of a malignant cell, *in vivo* or *ex vivo* (p. 11, 0048).

As specifically drawn to claims 6-8, one cannot extrapolate the teaching of the specification to the scope of the claims because the art of protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are

limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding (such as amino acids 56-100 of SEQ ID NO:1) will certainly be among the most conserved (see Bowie et al, Science, 247:1306-1310, 1990, (col 2, p. 1306). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed. Although the specification teaches that functional homologs of the protein fragments are those that maintain at least some activity of the protein fragment, that activity is not defined, nor are the substitutions, additions or deletions that will permit the invention to function as claimed. The artisan is left to random experimentation in order to determine which residues may be altered and how they may be altered in order to produce an altered homolog that will function as claimed and contemplated. Random experimentation is undue. Although it is appears that binding specificity of the disclosed fragment is determined by amino acids 56-100 of SEQ ID NO:1, the exquisite sensitivity of binding proteins to alterations of even a single amino acid is well known in the art. For example, although drawn to the antibody arts, the following is clearly relevant to the instant major groove binding function of amino acids 56-100 of SEQ ID NO:1. The teaching of Gussow et al (Methods in Enzymology, 1991, 203:99-121) is clearly relevant to the instant rejection. Gussow et al specifically teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen

binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original MAb and further disclose that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as was demonstrated by mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) which restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Further, even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of antigen-binding function. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein and the effect of 40%, 20%, 10%, 2% alterations on binding protein function of a 44 amino acid fragment that inhibits cellular proliferation by binding to the major groove of target DNA cannot be predicted. Further, even if the altered fragment were to bind to the major groove, it cannot be predicted, given the above, that the fragment would bind at the same site or would be useful to inhibit

cellular proliferation as contemplated. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein These references demonstrate that even a single amino acid substitution will often dramatically affect the binding activity and characteristics of a protein. Clearly, with a 40%, 20%, 10%, 2% dissimilarity, to amino acids 56-100 of SEQ ID NO:1, the function of the claimed polypeptide fragment could not be predicted, based on sequence similarity with amino acids 56-100 of SEQ ID NO:1, nor would it be expected to be the same as that of amino acids 56-100 SEQ ID NO:1. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of

gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Rudikoff, Gussow et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 40%, 20%, 10%, 2% dissimilarity, to amino acids 56-100 of SEQ ID NO:1, the function of the claimed polypeptides could not be predicted, based on sequence similarity with amino acids 56-100 of SEQ ID NO:1, nor would it be expected to be the same as that of amino acids 56-100 of SEQ ID NO:1.

Further, Claims 1, 2, 4 are drawn to a TBX5 protein fragment comprising a translated 5' T-box sequence capable of binding to the major groove of target DNA and lacking a translated 3' T-box sequence capable of binding to the minor groove

of target DNA, said fragment derived from a human, wherein the fragment lacks the sequence comprising amino acid 198 to the C-terminus of SEQ ID NO:1. The specification teaches that the inventors discovered that TBX5 inhibits cellular proliferation and that the 5' TBX5 T-box sequence is necessary for anti-proliferative effect (p. 4, 0019) and reports that the human TBX5 protein is the same as that reported by Basson et al, PNAS, 96:2919-2924 (p. 4, 0022). It is preferred that the TBX5 protein fragment is derived from a mammalian species such as rats, mice and rabbits, farm animals, pigs, horses and that the fragment may also include naturally occurring functional mutational or allelic variants (para bridging pgs 5-6). The invention includes functional homologs of the protein fragments described wherein homologs of a protein fragment are considered to be functional homologs if the homolog maintains at least some activity of the protein fragment (p. 6, 0028). The homolog can be a substitution, addition or deletion variant (p. 6, 0030).

As specifically drawn to claims 1, 2, 4 Examiner takes note of the well known lack of 100% identity of species homologs to each other. One cannot extrapolate the teaching of the specification to the scope of the claims because f the known unpredictability of the art of protein chemistry set forth above. It would be expected that species homologs would differ from the human TBX5 protein amino acids 56-100 as well as the entire SEQ ID NO:1 disclosed by 40%, 20%, 10%, 2%. Further, the claims are drawn to not only species homologs, but also to allelic variants of human SEQ ID NO:1. Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlag, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus

on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Clearly, the number of mutational differences in allelic variants cannot be predicted and again, allelic variants of human SEQ ID NO: 1 would be expected to differ from TBX5 protein by any number of mutations and it would be reasonable to assume that allelic variants would include those that differ from human TBX5 protein amino acids 56-100 as well as the entire SEQ ID NO:1 by 40%, 20%, 10%, 2%. For the reasons set forth above and given the teachings of Bowie et al, Burgess et al, Bork et al, Rudikoff et al, Gussow et al, it could not be predicted, nor would it be expected that the broadly claimed fragments would function as claimed or as contemplated.

The specification provides insufficient guidance with regard to these issues drawn to claims 1,2, 4, 6-8 and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed fragment variants would function as claimed or as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 5-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Basson et al (PNAS, 1999, 2919-2924, IDS item) as evidenced by the Specification at page 4, and Li et al (Nat. Gen., 1997, 15:21-29, IDS item).

The claims are drawn to an isolated TBX5 protein fragment comprising a translated 5'T-box sequence capable of binding to the major groove of target DNA and lacking a translated 3' T-box sequence capable of binding to the minor groove of target DNA, wherein the protein fragment is derived from a human, wherein it comprises amino acids 56-100 of SEQ ID NO;1, wherein the protein fragment lacks the sequence comprising approximately amino acid 198 to the C-terminus of SEQ ID NO;1, wherein the sequence comprises an amino acid sequence at least about 60%, 80%, 90%-98% identical to amino acids 56-100 of SEQ ID NO:1.

The specification admits on the record that the human TBX5 nucleotide coding sequence and translated amino acid sequence were deposited in the GenBank Data Base as Accession no. U80987. A review of Genbank revealed that the information was deposited on July 26, 1997, see attached search report.

Basson et al teach a nonsense mutation detected in individuals affected by Holt-Oram syndrome which is truncated at codon 196 which encodes a human TBX5 fragment of 196 amino acids which is 100% identical to amino acids 1-196 of SEQ ID NO:1. Given the known nucleotide and polypeptide sequences, one would immediately envision the TBX5 fragment (see Table 1, p. 2921). All of the limitations of the claims are met.

Li et al teach a human TBX5 nonsense mutation detected in individuals affected by Holt-Oram syndrome which has a C-A change at nucleotide 1,243 which

results in a TAA stop codon and which encodes a polypeptide which is truncated at amino acid 194. Both the nucleotide sequence and the encoded polypeptide sequence are disclosed in Figure 2, page 23. Given the disclosed nucleotide and polypeptide sequences, one would immediately envision the TBX5 fragment. Although the reference does not specifically teach that the sequence of the fragment is identical to SEQ ID NO:1, given that the encoded polypeptide is human TBX5, given that Basson et al, Supra, specifically refers to the Li paper as drawn to human TBX5 mutations (see Table 1) the claimed fragments appear to be the same as the prior art fragment, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
June 29, 2003